

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

Sub
C2
BP

23. A composition comprising a recombinant polynucleotide encoding a Receptor Internalization and Degradation (RID) complex and a pharmaceutically acceptable excipient, where the RID complex includes a RID α polypeptide and a RID β polypeptide.

24. (Twice amended) A recombinant adenovirus vector comprising a polynucleotide encoding a Receptor Internalization and Degradation (RID) complex having a RID α polypeptide and a RID β polypeptide, which RID complex is operably linked to a promoter, wherein the adenovirus is replication defective and wherein the polynucleotide is expressed upon infection of a eukaryotic cell with the adenovirus.

Remarks

Applicant thanks Examiners Lee and Hauda for the courtesies extended in the telephonic interview of December 13, 2000.

Claims 1, 2, 4, 6, 7, 20, 23-24, 27, 29, 30, and 23-25 remain pending after the above claim amendments. Claims 1, 3, 6, 7, 10, 12, 17, 19, 23, and 24 have been amended and claims 2, 5, 8, 9, 11, 15, 16, 18, 21, and 22 have been cancelled to more particularly point out and distinctly claim the invention. The claim amendments are offered in part to make clear that the claimed methods are directed to direct treatment of recombinant polynucleotides encoding a RID complex to target cells.

Applicant notes with appreciation the withdrawal of the rejection of claims 1-25 as being vague and indefinite, and the rejection of claim 23 as being vague and indefinite.

Applicant also notes with appreciation the allowability of claims 4, 7, 13-14, 17-22 and 25 if rewritten in independent form, including all of the limitations of the base claim and any intervening claims. However, it is noted that claim 17 is an independent claim and that claims 18-22 are all ultimately dependent only on claim 17. Applicant also notes that claim 17 as amended has additional limitations than when examined and found allowable, and therefore should still be allowable. Therefore, applicant respectfully requests the allowance of claims 17-22.

Rejections under 35 U.S.C. 112

Applicant notes with appreciation the withdrawal of the rejection of claims 1-3, 5-12, 14-19, and 21-24 under 35 U.S.C. 112, first paragraph (at page 2 of the Office Action), along with the holding that the arguments and declaration of April 12, 2000 were persuasive with regard to the enablement of the specification with effective dosage and stability issues (at page 12-13 of the Office Action). However, the following new rejections under 35 U.S.C. 112, first paragraph were entered.

Claims 1, 8-10, 14-17 and 21-23 stand rejected under 35 U.S.C. 112, first paragraph, as lacking enablement for “any and all routes of administration of a RID peptide complex for the treatment of any and all diseases/disorders treated by inhibiting or decreasing apoptosis in any and all patient.” Enablement is also asserted to be lacking because “... the specification does not provide a correlation between RID delivery to the alleviating degenerative disease or an immunodeficiency disease” (page 4 of the Office Action) and that particulars of route of administration, dosages, and treatment protocols (page 5). Applicant respectfully requests reconsideration and withdrawal of the rejection in light of the claim amendments and the following remarks.

Applicant first notes that claims 8, 9, 15, 16, 21 and 22 are cancelled. This rejection is therefore moot with regard to those claims. Applicant also notes that claim 1 is not directed to treatment of a patient. Therefore, the asserted disease treatment enablement deficiencies would not apply to claim 1. In this regard, applicant points out that the claims directed to treatment of cells of a patient (claims 10, 14, and 17) do not require the alleviation of disease symptoms or the reduction in disease. Those claims only require a decrease in apoptosis in the treated cells. Although the claims do not require that such a treatment can cure or alleviate symptoms of any disease, the claimed reduction in apoptosis could nonetheless be useful for treating disease, e.g., in combination with other treatments, etc. Applicant also notes that the amended claims are all limited to direct administration of cells with a polynucleotide encoding the RID complex, which is abundantly enabled in the specification, e.g., in the examples (see following discussion of examples).

With regard to the asserted lack of enablement for particular routes of administration, dosages and treatment protocols, applicant first notes that the present Office Action, at pp. 12-13, found that such parameters are enabled based on the arguments and declaration filed April 12, 2000. Applicant also points out that the claims as amended clearly require that the polynucleotide encoding the RID complex be administered directly to the cells, and contend that the administration, dosage and treatment protocols could be determined for any particular cell treatment without undue experimentation, particularly since the specification provides several examples that give dosages and provides protocols for administration to cells. See, e.g., in Example 2, where plasmids expressing RID component polypeptides are used to transfect mammalian cells, and the effect of the presence and absence of the RID complex upon apoptosis of the cells is demonstrated; in Example 3, where an adenovirus vector was used to transfect human cells to demonstrate clearing of Fas; in Example 4, where human A549 cells were infected with viral vectors that were positive or negative for the expression of RID complex polypeptides, and clearing of Fas from the cell surface was measured; in Example 5, where human MCF7 cells were infected with wild-type or mutant adenovirus to demonstrate that signal receptors are degraded in lysosomes; in Example 6, where COS cells were transiently transfected with plasmids containing various

RID complex components and it was shown that Fas was cleared from the surface of the cells by the complete RID complex; in Example 7, where lymphocytes withdrawn from mice infected with influenza virus were activated and incubated with RID⁺ and RID⁻ mouse cells to show that RID inhibited CTL cell killing through the Fas pathway; and in Example 8, where human HeLa cells infected with viral RID polynucleotides and with the 231-10 vector RID polynucleotides showed the internalization and destruction of Fas and TNFR1. See also Wold declaration filed with the response of April 6, 2000 at page 4-5, discussing these parameters based on the examples in the specification.

Applicant notes that claims 1, 3, 4, 6, 7, 10, 12, 13 and 14 include embodiments where the target cells are treated *in vivo*. Although there is no example in the specification that shows an *in vivo* application, the skilled artisan, upon reviewing the specification, would understand that *in vivo* applications are fully enabled. This is particularly apparent from Example 9, where the 231-10 vector, expressing the RID complex, was administered to human cancer cells, which were then transplanted into mice after 48 hours. The 231-10 treatment prevented the cells from being rejected, indicating that the RID complex removed Fas and TNFR1 from these cells sufficiently to prevent natural killer (NK)- and cytotoxic T lymphocyte (CTL)-mediated killing of these cells.

Given the results of the Example 9 experiment, and based on what is known about transplant rejection as well as what is disclosed in the instant specification about the ability of the RID complex to remove Fas and TNFR1 from cells, the skilled artisan would understand that vectors encoding the RID complex would prevent NK- and CTL- mediated apoptosis of transplanted tissue when the tissue is treated *in vivo* after transplantation. This is because (a) it is well known (and disclosed in the specification at page 30, lines 25-28) that transplant rejection begins after 1-2 days by NK cells and macrophages, and after 5-7 days specific CTLs form which play a major role in rejection; and (b) the specification establishes that treatment of cells with a polynucleotide encoding the RID complex eliminates Fas and TNFR1 from the cells within 1-2 days. The latter point is established, e.g., in Example 3, where the RID complex-overexpressing adenovirus *pm760* and other RID-expressing adenoviruses completely cleared Fas from human adenocarcinoma cells after 28 hours (page 20, lines 4-21); in Example 4, showing a similar effect after 26 hours (p. 21, lines 3-16); in Example 5, showing the removal of Fas from the cell surface within 19 hours (p. 21, lines 21-32); and in Example 8, where RID-expressing adenoviruses progressively eliminated TNFR1 from cells between 18 and 30 hours such that virtually no TNFR1 could be detected after 30 hours. Thus, the skilled artisan would understand that the RID vector would effectively eliminate the death receptors (e.g., Fas and TNFR1) from the transplant tissue in sufficient time to prevent the NK- and CTL-mediated apoptosis that characterizes transplant rejection.

To further point out the state of the art with regard to the use of gene therapy for transplantation, applicant points to Giannoukakis et al., 1999, *Gene Therapy* 6, 1499-1511, included with this response,

which thoroughly reviews that technology. As noted in the Abstract of Giannoukis et al., "Vectors have been developed which can optimally transfer relevant genes to tissues and organs. Interventions aimed at promoting tissue preservation before transplantation, prevention of oxidative stress and immunological rejection have recently become attractive using viral and nonviral delivery vehicles." Efforts have also been directed towards preservation of organ and tissue integrity and function after the organ has been removed and before it has been transplanted into the recipient, and also immediately after the transplant when reperfusion occurs. Many of the factors that contribute to the ischemia/reperfusion injury of organs is mediated by cytokines and immune cells that induce apoptosis of organ cells. In the instant invention, the RID polynucleotide would be administered to the organ *ex vivo*, for example through the use of 231-10, then the organ would be transplanted into the patient. See, e.g., the use of adenovirus vectors expressing such proteins as superoxide dismutase or CTLA-4Ig which have been used to infect organs in vitro and to provide some protection to the organ following transplantation into animal models (see Giannoukis et al. at p. 1502, left column and p. 1505, left column). Alternatively, the organ could be treated with the vector *in vivo* after transplantation. The skilled artisan would know that the adenoviral vector could be delivered to the organ after transplantation rather than before transplantation, and that the few minutes difference between the *ex vivo* treatment and the *in vivo* treatment would not be expected to affect the success of the treatment. Indeed, post-transplantation ICAM-1 antisense therapy has been shown to lead to prolongation of allogeneic islet survival. Giannoukis et al. at 1502, right column. Thus, given the length of time required for transplant rejection to occur, and the demonstration of the rapidity with which the RID complex vectors remove Fas and other death ligands, the skilled artisan would know that *ex vivo* or *in vivo* treatment of the transplanted cells would have equivalent efficacy.

There is also no reason to doubt that treating leukocytes *in vivo* by injection of a RID complex vector such as 231-10 into the bloodstream (where leukocytes are circulating) would be effective in removing the death receptors from those cells and thus inhibit apoptosis of those cells, e.g., in cancer patients.

Thus, the skilled artisan would have no reason to doubt that the methods claimed in claims 1, 3, 4, 6, 7, 10, 12, 13 and 14 are effective and fully enabled for *in vivo* applications.

Based on the above discussion, the rejected claims are clearly enabled as amended. Applicant therefore respectfully requests reconsideration and withdrawal of the rejection of claims 1, 8-10, 14-17 and 21-23 under 35 U.S.C. 112, first paragraph.

Claims 1-7, 10-14, 17-20 and 24-25 stand rejected under 35 U.S.C. 112, first paragraph as lacking enablement for any and all routes of administration, and treating any and all patients suffering from any and all diseases/disorders such as degenerative disease or immunodeficiency disease. Applicant

respectfully requests reconsideration and withdrawal of this rejection in light of the claim amendments, the discussion of the rejection of claims 1, 8-10, 14-17 and 21-23 above, and the following remarks.

The apparent primary objection to these claims is that targeting gene therapy treatments to specific cell types or locations is asserted to be an unpredictable art. Applicant first points out that the current claims are now limited to the direct treatment of cells. It is believed that this would render the objection to the targeting aspects of the current claims moot, since the targeted cells are directly treated. Further, at the middle of page 8, the current Office Action states that the claims are enabled for inhibiting apoptosis *in vitro* where the claim is specifically directed to contacting a cell line with an expression vector comprising a nucleic acid encoding RID complex in operable linkage with a promoter. It is also noted that claims 1, 3, 4, 6, 7, 24 and 25 are not directed to treatment of patients. Thus, those claims should not be affected by any aspect of this rejection that relates to treatment of disease. See the discussion of the rejection of claims 1, 8-10, 14-17 and 21-23 above for further elaboration of this point. For the above reasons, applicant respectfully requests reconsideration and withdrawal of the rejection of claims 1-7, 10-14, 17-20 and 24-25 under 35 U.S.C. 112, first paragraph.

Claims 4, 13, 20, and 25 stand rejected under 35 U.S.C. 112, first paragraph as failing to provide an enabling disclosure. It is asserted that the 231-10 vector is not obtainable by any repeatable method set forth in the specification, or is otherwise not available to the public. Applicant again maintains that the 231-10 vector can be made by the skilled artisan, not only by the methods disclosed in the specification, but also by any of a number of methods that would be readily apparent to the skilled artisan, given that the specification discloses the nucleotide sequence of the plasmid in Figure 27, as well as SEQ ID NO:5. The skilled artisan would know that the method disclosed in Example 10 is not the only way to produce the plasmid with the sequence of SEQ ID NO:5. For example, the skilled artisan could, without undue experimentation, simply obtain an adenovirus serotype 5, which is available from the American Type Culture Collection (ATCC), make the proper deletions from that virus by well established methods, create an E3 transcription unit identical to the *pm734.1* E3 unit by cloning it from the adenovirus 5 E3 unit, recombine them in the proper sequence, and create the proper missense mutations in the *adp* gene, all methods that are well within the ability of any skilled molecular biologist without undue experimentation. Then, the skilled artisan could easily clone the CMV promoter from a cytomegalovirus, also available from ATCC, and clone that in the proper place, which is easily performed without undue experimentation, to create the 231-10 vector. All of the above methods could be performed using materials available from ATCC without undue experimentation. The skilled artisan would also know that there are many other ways that the sequence given in SEQ ID NO:5 could be created using well known methods such as those

described above. In light of these remarks, applicant respectfully requests reconsideration and withdrawal of the rejection of claims 4, 13, 20, and 25 under 35 U.S.C. 112, first paragraph.

Claims 1-22 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite. It is asserted that the step "an effective amount of a Receptor Internalization and Degradation complex" does not correlate with the inhibition of apoptosis. Applicant notes that claims 1, 10 and 17 (to which the other rejected claims depend) have been amended to more definitely make the correlation between "effective amount" and inhibiting apoptosis. In light of these claim amendments, applicant respectfully requests reconsideration and withdrawal of the rejection of claims 1-22 under 35 U.S.C. 112, second paragraph.

Rejections under 35 U.S.C. 102

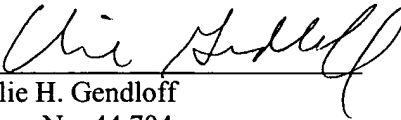
Claims 1-3, 5, 10-13 and 24 stand rejected under 35 U.S.C. 102(b) as being anticipated by Dimitrov et al. (August 1997), *J. Virol.* 71:2830-2837. Applicant respectfully requests reconsideration and withdrawal of this rejection because the reference was published after the priority date of July 7, 1997 (U.S. Provisional Application No. 60/088,993) and is therefore unavailable as prior art. Applicant also states in the enclosed declaration under 37 C.F.R. 1.132 that the work in that publication is the author's own work.

Claims 1-3, 5-6, 8-12, 15-16 and 24 stand rejected under 35 U.S.C. 102(a) as being anticipated by Krajcsi et al. (August 1996), *J. Virol.* 70:4904-4913. In response to this rejection, applicant has submitted a declaration under 37 C.F.R. 1.132 stating that the cited reference represents applicant's own work and therefore should not be considered as prior art.

Claims 1-3, 5, 8-12, 15-16 and 24 stand rejected under 35 U.S.C. 102(b) as being anticipated by Stewart et al., 1995, *J. Virol.* 69:5871-5881. Applicant respectfully requests reconsideration and withdrawal of this rejection based on the following discussion. The PTO states that Stewart et al. teaches that the RID complex is localized to the plasma membrane, that both proteins are required for plasma membrane localization, that certain adenovirus mutants confer preventive or protective functions, and that the RID complex interferes with the function of membrane-associated proteins that participate in TNF signaling. However, the PTO correctly does not state that Stewart et al. treats a cell with a RID complex to inhibit apoptosis; nor does Stewart et al. suggest that such a treatment would be successful. Since Stewart et al. does not disclose the claimed method, applicant asserts that it does not anticipate the claims. Based on the above discussion, applicant urges the reconsideration and withdrawal of the rejection of claims 1-3, 5, 8-12, 15-16 and 24 under 35 U.S.C. 102(b).

Based on the above claim amendments and discussion, applicant believes that the claims are in condition for allowance. Should there be any further issues preventing such a finding, applicant respectfully requests that the examiner contact the undersigned attorney.

Respectfully submitted,



Elie H. Gendloff
Reg. No. 44,704
Howell & Haferkamp, L.C.
7733 Forsyth Boulevard, Suite 1400
St. Louis, Missouri 63105
(314) 727-5188

January 11, 2001